Doxepin for insomnia

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Low-dose doxepin—3 mg and 6 mg—has demonstrated efficacy for insomnia characterized by frequent or early-morning awakenings and an inability to return to sleep (Table 1). FDA-approved in March 2010, doxepin (3 mg and 6 mg) is only the second insomnia medication not designated as a controlled substance and thus may be of special value in patients with a history of substance abuse.

Clinical implications
Ramelteon, the other hypnotic that is not a controlled substance, is indicated for sleep initiation insomnia (ie, inability to fall asleep). In contrast, low-dose doxepin is for patients with sleep maintenance insomnia, which is waking up frequently or early in the morning and not falling back asleep.

How it works
Doxepin’s mechanism of action for treating depression and insomnia remains unknown. The antidepressant effect of doxepin is thought to result from inhibition of serotonin and norepinephrine reuptake at the synaptic cleft. Animal studies have shown anticholinergic and antihistaminergic activity with doxepin.

Doxepin is a potent histamine antagonist—predominantly at the H1 receptor—and its binding potency to the H1 receptor is approximately 100-times higher than its binding potency for monoamine transporters (serotonin and norepinephrine).

Brain histamine is believed to be 1 of the key elements in maintaining wakefulness, and the activation of the H1 recept-
tor is thought to play an important role in mediating arousal. Blockade of the H1 receptor by doxepin likely plays a role in reducing wakefulness. Typically, therapeutic doses of antidepressants with anti-histaminergic properties, such as doxepin at antidepressant doses, amitriptyline, or desipramine, do not selectively block H1 receptors, but act at cholinergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors, which can cause adverse effects. However, low doses of doxepin (1, 3, and 6 mg) can achieve selective H1 blockade. Patients taking >25 mg/d of doxepin may report clinically significant anticholinergic effects.

**Pharmacokinetics**

When doxepin, 6 mg, was administered to healthy, fasting patients, time to maximum concentration (Tmax) was 3.5 hours. Peak plasma concentration (Cmax) increased in a dose-related fashion when doxepin was increased from 3 mg to 6 mg. Doxepin, 6 mg, taken with a high-fat meal resulted in area under the curve increase of 41%, Cmax increase of 15%, and almost 3-hour delay in Tmax. Therefore, to prevent a delay in onset of action and to minimize the likelihood of daytime sedation, doxepin should not be taken within 3 hours of a meal.

Doxepin is metabolized primarily by the liver’s cytochrome P450 (CYP) 2C19 and CYP2D6 enzymes; CYP1A2 and CYP2D6 are involved to a lesser extent. If doxepin is coadministered with drugs that inhibit these isoenzymes, such as fluoxetine and paroxetine, doxepin blood levels may increase. Doxepin does not seem to induce CYP isoenzymes. This medication is metabolized by demethylation and oxidation; the primary metabolite is nordoxepin (N-desmethyldoxepin), which later undergoes glucuronide conjugation. The half-life is 15 hours for doxepin and 31 hours for nordoxepin. Doxepin is excreted in urine primarily as glucuronide conjugate.

Coadministration with cimetidine, an inhibitor of CYP isoenzymes, could double the doxepin plasma concentration; therefore, patients taking cimetidine should not exceed 3 mg/d of doxepin.

**Efficacy**

Doxepin reduced insomnia symptoms in 3 pilot studies at doses of 10, 25, and 50 mg, and in 2 phase III randomized, double-blind, placebo-controlled clinical trials using 1, 3, and 6 mg (Table 2, page 74). Clinical studies lasted up to 3 months.

In the first phase III trial, 67 patients, age 18 to 64 with chronic primary insomnia, were randomly assigned to placebo or 1 mg, 3 mg, or 6 mg of doxepin for 2 nights. All patients received all treatments, and each treatment was followed by 8 hours of polysomnography ( PSG evaluation in a sleep laboratory. In this study, patients taking doxepin at all doses achieved improvement in objective (PSG-defined) and subjective (patient-reported) measures of sleep duration and sleep maintenance. Wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE) improved with all doxepin doses, and wake time during sleep (WTDS)—which was the primary study endpoint—decreased with 3 mg and 6 mg doses, but not with 1 mg or placebo. In addition, PSG indicators of early-morning awakenings (terminal insomnia) were reduced, as shown by an increase in SE during the final third of the night and the 7th and 8th hours of sleep (1, 3, and 6 mg doses) and a reduction in wake time after sleep (WTAS) during the final third of the night (6 mg only). The effects on sleep duration and maintenance were more robust with 3 mg and 6 mg doses. Improved sleep onset was seen only with the 6 mg dose. Next-day alertness was assessed using the Visual Analogue Scale (VAS) for sleepiness, and the Digit-Symbol Substitution Test (DSST) and the Symbol-Copying Task (SCT) for psychomotor function. No statistically significant differences were found among placebo and any of the doxepin doses on the VAS, DSST, or SCT.

Doxepin was well tolerated. Reported adverse events were mild or moderate. Headaches and somnolence were report-
Clinical Point
Doxepin is better tolerated at hypnotic doses than at antidepressant doses, although direct comparative studies are not available.

ed by >2% of patients. The incidence of adverse events, including next-day sedation, was similar to that of placebo. Additionally, there were no spontaneous reports of anticholinergic side effects, which are associated with higher doxepin doses.\(^4\)

The second phase III trial examined safety and efficacy of 1, 3, and 6 mg doxepin in patients age ≥65.\(^5\) Seventy-six adults with primary insomnia were randomly assigned to receive placebo or doxepin for 2 nights; all patients received all treatments, and each treatment was followed by an 8-hour PSG. Patients taking any doxepin dose achieved objective and subjective improvement in sleep duration and sleep maintenance, which lasted into the final hours of the night. WTDS (primary study endpoint), WASO, TST, and overall SE improved at all doxepin doses compared with placebo, and WTAS and SE at hours 7 and 8 improved at doxepin doses of 3 mg and 6 mg compared with placebo. These findings suggest that doxepin, 3 mg and 6 mg, can help older insomnia patients with early morning awakenings.

In this study, no statistically significant differences were found among placebo and any doxepin doses on VAS, DSST, or SCT or next-day residual sedation. The incidence of side effects was low and similar to that of placebo. Adverse events were mild or moderate; 1 incident of chest pain was reported, but it was determined not to be of cardiac origin and not related to study drug. There were no spontaneous reports of anticholinergic side effects associated with higher doses of doxepin. There were no reports of memory impairment.\(^5\)

Tolerability
Clinical studies that evaluated the safety of doxepin lasted up to 3 months. Somnolence/sedation, nausea, and upper respiratory tract infection were reported by >2% of patients taking doxepin and were more common than in patients treated with placebo.\(^1\) All reported adverse events were mild to moderate.

### Table 2

**Evidence of effectiveness of doxepin for insomnia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Dosages</th>
<th>Results</th>
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<tbody>
<tr>
<td>Roth et al, 2007(^4); phase III, randomized, multi-center, double-blind, placebo-controlled, 4-period crossover, dose-response study</td>
<td>67 patients age 18 to 64 with chronic primary insomnia</td>
<td>1, 3, or 6 mg given once daily at bedtime for 2 nights</td>
<td>Improvement vs placebo in PSG-defined WASO, TST, SE, and WTAS during the final third of the night. 6-mg dose significantly reduced subjective latency to sleep onset. Safety profile of all 3 doses was comparable to placebo. No difference in residual sedation</td>
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<tr>
<td>Scharf et al, 2008(^5); phase III, randomized, multi-center, double-blind, placebo-controlled, 4-period crossover, dose-response study</td>
<td>76 patients age ≥65 with primary insomnia</td>
<td>1, 3, or 6 mg at bedtime for 2 nights</td>
<td>Reduction vs placebo in WTDS and WASO at all 3 doses. Increase in TST and SE at all 3 doses. No difference in number of awakenings after sleep onset and latency to persistent sleep at all 3 doses. WTAS was reduced only at 3 and 6 mg doses. Patient-reported WTAS was decreased at all doses. Patient-reported latency to sleep onset decreased only with 6 mg. Safety profile of all 3 doses was comparable to placebo and there were no differences among placebo and all 3 doses doxepin in next-day sleepiness or psychomotor function</td>
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PSG: polysomnography; SE: sleep efficiency; TST: total sleep time; WASO: wake after sleep onset; WTAS: wake time after sleep; WTDS: wake time during sleep

_Source:_ References 4, 5

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Low-dose doxepin may be an effective option for patients with insomnia characterized by difficulties with sleep maintenance. At 3 and 6 mg, doxepin appears to be effective and well tolerated. Doxepin is not designated as a controlled substance. Unlike GABA agonists, low-dose doxepin appears to selectively block histaminergic action; it is essentially inactive at benzodiazepine receptor sites.
Dosing
In adults, the recommended hypnotic dose for doxepin is 6 mg taken 30 minutes before bedtime. For patients age ≥65, the recommended starting hypnotic dose is 3 mg 30 minutes before bedtime, which can be increased to 6 mg if indicated.1

References